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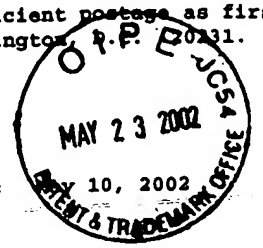

Date: May 10, 2002

Dennis P. Tramaloni
(Print Name)

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1614

Paul Hebeisen, et al.

Serial No.: 10/092,751

Filed: March 07, 2002

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For: **PIPERAZINE DERIVATIVES**

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May 10, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Great Britain	0106177.9	March 13, 2001

Respectfully submitted,

Dennis P. Tramaloni
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#3

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

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Signed Andrew Gerry

Dated 28 JAN 2002

Patents Form 1/77

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The Patent Office

No fee

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Request for grant of a patent

13 MAR 2001

The Patent Office

Concept House
Cardiff Road
Newport
South Wales, NP10 8QQ

1. Your reference: P15189GB-KR/mf

2. Patent application number *(The Patent Office will fill in this part)*: **0106177.9**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

F. Hoffmann-La Roche AG
124 Grenzacherstrasse
CH-4070 Basle
Switzerland

Patents ADP number *(if you know it)*: 6505804001

If the applicant is a corporate body, give the country/state of its incorporation: SWITZERLAND

Vernalis Research Limited
Oakdene Court
613 Reading Road
Winnersh, Wokingham
RG41 5UA
United Kingdom

Patents ADP number *(if you know it)*: 7915184001

If the applicant is a corporate body, give the country/state of its incorporation: UNITED KINGDOM

4. Title of the invention: Piperazine Derivatives

5. Name of your agent *(if you have one)*: Forrester Ketley & Co.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:
Forrester House
52 Bounds Green Road
London N11 2EY

Patents ADP number *(if you know it)*: 133001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent based on the basis of this application

Forrester Ketley & Co.

Signature

Date
13 March 2001

Forrester Ketley & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom — Kate RICHARDSON — (020) 8889 6622

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F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

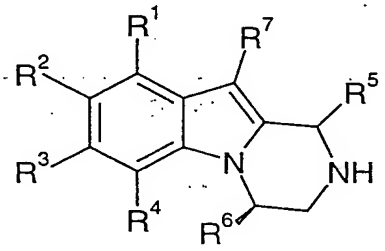
Vernalis Research Limited, England

Case 20858

Piperazine Derivatives

The present invention relates to new piperazine derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

The invention is concerned particularly with compounds of formula I and their pharmaceutically usable salts, solvates and esters



(I)

wherein

R^1, R^2, R^3 and R^4 are independently selected from hydrogen, halogen, hydroxy, alkyl, cycloalkyl, arylalkyl, aryl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, nitro, cyano, alkoxycarbonyl, aryloxycarbonyl, mono- and di-alkylaminocarbonyl, alkylcarbonylamino, carboxy or heterocyclyl; with the proviso that at least one of the moieties R^1, R^2, R^3 and R^4 is not hydrogen.

R^5 is hydrogen, alkyl or cycloalkyl;

R^6 is alkyl or cycloalkyl;

R^7 is hydrogen, halogen, alkyl, cycloalkyl, hydroxyalkyl, carboxyalkyl, carbamoylalkyl, alkoxycarbonylalkyl, aryloxycarbonylalkyl, formyl, alkylcarbonyl, alkoxy or alkylthio;

and their pharmaceutically acceptable salts, solvates and esters.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, *"Obesity: Trends and Treatments"*, Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes, particularly type II diabetes, (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (XENICAL®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve

abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, 96, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, 141, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, 113, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, 116, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, 133, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, 374, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, 36, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as antidepressants and antibiotics, e.g. 1,2,3,4 include 1,2,3,4-tetrahydroppyrazino[1,2-a]indoles and ethyl 1-(2-aminoethyl)indole-2-carboxylates (Rajur et al. (1989) Indian J. Chem., 28B(12), 1065-1068), tricyclic pyrazidole analogs (Grinev et al. (1984), Khim. Farm.Zh. 18(2), 159 – 163), derivates of 1-methylamino-9-methyl-1,2,3,4-tetrahydrocarbazole (Andreeva et al. (1976), Khim.Farm.Zh., 10(11), 46 – 49), and mitomycin analogues (Yamada et al. (1972), Agr. Biol. Chem., 36(1), 106 – 111) are structurally different. Further, US Patent No. 3,317,524 discloses structurally different 1,2,3,4-tetrahydro-pyrazino[1,2-a]indoles as anti-inflammatory agents, as central nervous system depressants, as analgesics and as anti-convulsants.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for 5-HT_{2B} and/or 5-HT_{2C} receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting 5-HT_{2C} receptor ligands,

preferably 5-HT_{2C} receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-4 carbon atoms. Examples of straight-chain and branched C_1-C_8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, propyl and isopropyl. Particularly preferred are methyl and ethyl.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C_3-C_8 cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethylcyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, methylcyclohexyl, dimethyl-cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl and particularly cyclopentyl.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.butoxy and tert.butoxy, preferably methoxy and ethoxy.

The term “alkoxycarbonyl” refers to a group of the formula alkoxy-C(O)-, wherein the term “alkoxy” is as defined above.

The term “alkoxycarbonylalkyl” refers to a group of the formula alkoxy-C(O)-alkyl, wherein the terms “alkoxy” and “alkyl” are as defined above.

The term "aryloxy", alone or in combination, signifies a group of the formula aryl-O- in which the term "aryl" has the previously given significance. Phenyloxy is an example of such an aryloxy group.

The term “aryloxycarbonyl”, alone or in combination, refers to a group of the formula aryloxy-C(O)-, wherein the term “aryloxy” is as defined above.

The term "haloalkyl", alone or in combination, signifies an alkyl group as previously defined, wherein one or several hydrogen atoms, preferably one, two or three hydrogen

atom(s) have / has been replaced by halogen. Examples of haloalkyl groups are trifluoromethyl, pentafluoromethyl and trichloromethyl. Preferred examples are trifluoromethyl and difluoromethyl.

The term "haloalkoxy", alone or in combination, signifies an alkoxy group as previously defined, wherein one or several hydrogen atoms, preferably one, two or three hydrogen atom(s) have / has been replaced by halogen. Examples of haloalkoxy groups are trifluoromethoxy, difluoromethoxy and trichloromethoxy.

The term "hydroxyalkyl", alone or in combination, signifies an alkyl group as defined above, wherein one or several hydrogen atoms, preferably one, have / has been replaced by hydroxy.

The term "carbonyl", alone or in combination, refers to a group of the formula –C(O)-.

The terms "alkylcarbonyl" or "alkanoyl", alone or in combination, refer to a group of the formula alkyl-C(O)- with alkyl as defined above.

The term "alkylthio", alone or in combination, signifies a group of the formula alkyl-S- in which the term "alkyl" has the previously given significance, such as methylthio, ethylthio, n-propylthio, isopropylthio. Preferred are methylthio and ethylthio.

The term "arylthio", alone or in combination, signifies a group of the formula aryl-S- in which the term "aryl" has the previously given significance. Phenylthio is an example of such an arylthio group.

The term "sulphonyl", alone or in combination, signifies a group of the formula $-S(O)_2-$.

The term "sulfoxyl", alone or in combination, signifies a group of the formula -S(O)-.

The term "aryl", alone or in combination, signifies a phenyl group which optionally carries one to three substituents each independently selected from alkyl, alkoxy, halogen, carboxy, alkoxycarbonyl, aminocarbonyl, hydroxy, amino, nitro and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert.butoxyphenyl, 4-fluorophenyl, 2-chlorophenyl, 3-

chlorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-naphthyl. Preferred is phenyl.

The term "heterocyclyl", alone or in combination, signifies a saturated, partially unsaturated or aromatic 5- to 10-membered heterocycle, preferably a 5- or 6-membered ring which contains one to three hetero atoms selected from nitrogen, oxygen and sulphur. If desired, it can be substituted on one to three carbon atoms by halogen, alkyl, alkoxy, oxo etc. and/or on a secondary nitrogen atom (i.e. -NH-) by alkyl, cycloalkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e.=N-) by oxido, with halogen, alkyl, cycloalkyl and alkoxy being preferred. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrazoyl, imidazoyl (e.g. imidazol-4-yl and 1-benzyloxycarbonyl- imidazol-4-yl), pyrazoyl, pyridyl, pyrazinyl, pyrimidinyl, hexahydro-pyrimidinyl, furyl, thienyl, thiazolyl, oxazolyl, indolyl (e.g. 2-indolyl), quinolyl (e.g. 2-quinolyl, 3-quinolyl and 1-oxido-2-quinolyl), isoquinolyl (e.g. 1-isoquinolyl and 3-isoquinolyl), tetrahydroquinolyl (e.g.1,2,3,4-tetrahydro-2-quinolyl), 1,2,3,4-tetrahydroisoquinolyl (e.g. 1,2,3,4-tetrahydro-1-oxo-isoquinolyl) and quinoxalinyl.

The term "amino", alone or in combination, refers to the group $-NH_2$.

The term "halogen" or "halo" signifies fluorine, chlorine, bromine or iodine and preferably fluorine, chlorine or bromine and particularly fluorine and chlorine.

The term "carboxy", alone or in combination, signifies a -COOH group.

The term "carboxyalkyl" alone or in combination, signifies an alkyl group as previously described in which one hydrogen atom has been replaced by a carboxy group. The carboxymethyl group is preferred and particularly carboxyethyl.

The term "carbamoyl" refers to a group of the formula NH_2-C(O)-.

The term "carbamoylalkyl" refers to the group NH_2-C(O)-.alkyl, wherein the term "alkyl" is as defined above.

The term "formyl" refers to the group –CH=O.

Examples of pharmaceutically usable salts of the compounds of formula I are salts with physiologically compatible mineral acids such hydrochloric acid, sulphuric acid or

phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula I with free carboxy groups can also form salts with physiologically compatible bases. Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as the Na, K, Ca or tertramethylammonium salt. The compound of formula I can also be present in the form of zwitterions.

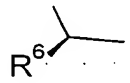
The invention expressly includes pharmaceutically suitable derivatives of the compounds of formula I. For example, the GOOH groups in R^1 to R^4 or R^6 can be esterified. The alkyl and aralkyl esters are examples of suitable esters. The methyl, ethyl, propyl, butyl and benzyl esters are preferred esters. The methyl and ethyl esters are especially preferred.

The compounds of formula I can also be solvated, e.g. hydrated. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration).

The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, 1994). The term "lipase inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to orlistat.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123.

Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

The compounds of formula I contain an asymmetric centre (indicated in formula (I) by 

).

The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbens or eluent).

In another preferred embodiment the invention refers to the above compounds, wherein at least two or three of the moieties R^1, R^2, R^3 and R^4 are not hydrogen.

In a preferred embodiment, the above compounds are characterized in that at least two of the moieties R^1, R^2, R^3 and R^4 are not hydrogen.

In a further preferred embodiment, the above compounds are characterized in that at least three of the moieties R^1, R^2, R^3 and R^4 are not hydrogen.

A preferred embodiment of the present invention refers to the above compounds, wherein R^1, R^2, R^3 and R^4 are independently selected from hydrogen, halogen, alkyl, alkoxy, haloalkoxy or haloalkyl.

In another embodiment, the above compounds are characterized in R^1, R^2, R^3 or R^4 are independently selected from hydrogen, halogen, alkyl, e.g. methyl and ethyl, alkoxy, e.g. methoxy, halomethyl, and halomethoxy, more preferably from hydrogen chloro, fluoro, bromo, trifluoromethyl, methyl, ethyl, methoxy and trifluoromethoxy.

Preferably, R^5 in the above compounds is hydrogen or alkyl, more preferably hydrogen or methyl, and most preferably hydrogen.

In a further preferred embodiment, the above compounds are characterized in that R^6 is alkyl or cycloalkyl, preferably alkyl, more preferably methyl or ethyl and most preferably methyl.

In another preferred embodiment, the above compounds are characterized in that R^7 is hydrogen, alkyl or alkoxy, more preferably hydrogen, methyl or methoxy, even more preferably hydrogen or methyl and most preferably R^7 is hydrogen.

The preferred compounds of formula (I) may be selected from the group consisting of

1. (R)-6-Ethyl-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
2. (R)-4-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
3. (R)-7-Bromo-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
4. (R)-7-Chloro-8-fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
5. (R)-4,8-Dimethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
6. (R)-7,9-Dichloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole
7. (R)-6-Fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
8. (R)-4,6-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
9. (R)-8-Fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
10. (R)-7-Chloro-10-methoxy-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
11. (R)-7-Chloro-4,6,10-trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole oxalate;
12. (R)-7-Bromo-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
13. (R)-4-methyl-6-trifluoromethoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
14. (R)-7-Chloro-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
15. (R)-7-Chloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
16. (R)-4,6,9-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
17. (R)-4,6,7-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
18. (R)-7-Chloro-4,6-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
19. (R)-4,8-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;

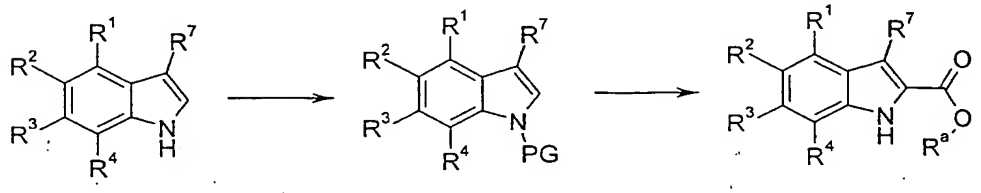
20. (R)-4,7-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride;
21. (R)-4,7,8-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole; and
22. (R)-7-Chloro-4,8-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole.

The most preferred compound may be selected from the group consisting of

1. (R)-6-Ethyl-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
2. (R)-4-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
3. (R)-4,8-Dimethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
4. (R)-4,6-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
5. (R)-7-Chloro-10-methoxy-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
6. (R)-7-Chloro-4,6,10-trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole oxalate; and
7. (R)-7-Chloro-4,6-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole.

Further, processes for the manufacture of the compounds according to formula I are an object of the present invention. The substituents and indices used in the following schemes have the significance given above unless indicated to the contrary.

Scheme 1:



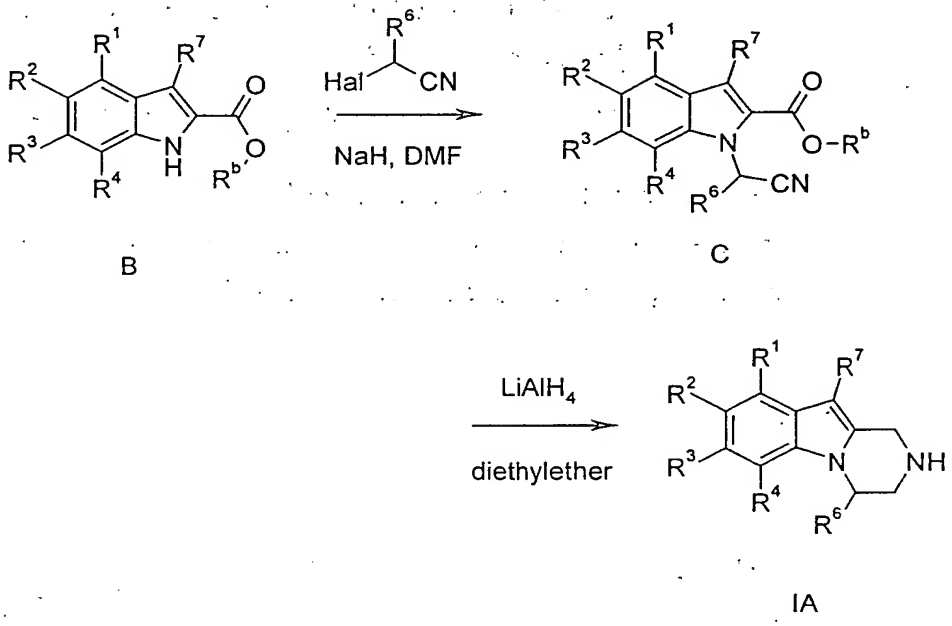
A B

Indoles of formula A can be prepared by methods known in the art, (e.g., T. L. Gilchrist, "Heterocyclic Chemistry", 1997 or "The Chemistry of Heterocyclic Compounds"

Vol. 25, 1972 or Joule, J. A. "Indoles, isoindoles, their reduced derivatives, and carbazoles". Rodd's Chem. Carbon Compd. 1997 or G. W. Gribble, J. Chem. Soc. Perkin I 2000, 1045).

Indole-2-carboxylates of formula B can be prepared by methods known in the art (see above) or alternatively from indoles of formula A by first protecting the indole nitrogen with a suitable protecting group (PG; e.g., tert-butoxycarbonyl (Boc)), treating the protected indole derivative with a suitable base under anhydrous conditions (e.g., with lithium 2,2,6,6-tetramethylpiperidide in THF), reacting the intermediate anion with a chloroformate (e.g. ethyl chloroformate) and removing the protecting group (e.g., by treatment with acid for the Boc protecting group). R^a in Scheme 1 is an alkyl group, preferably a lower alkyl group, preferably methyl or ethyl.

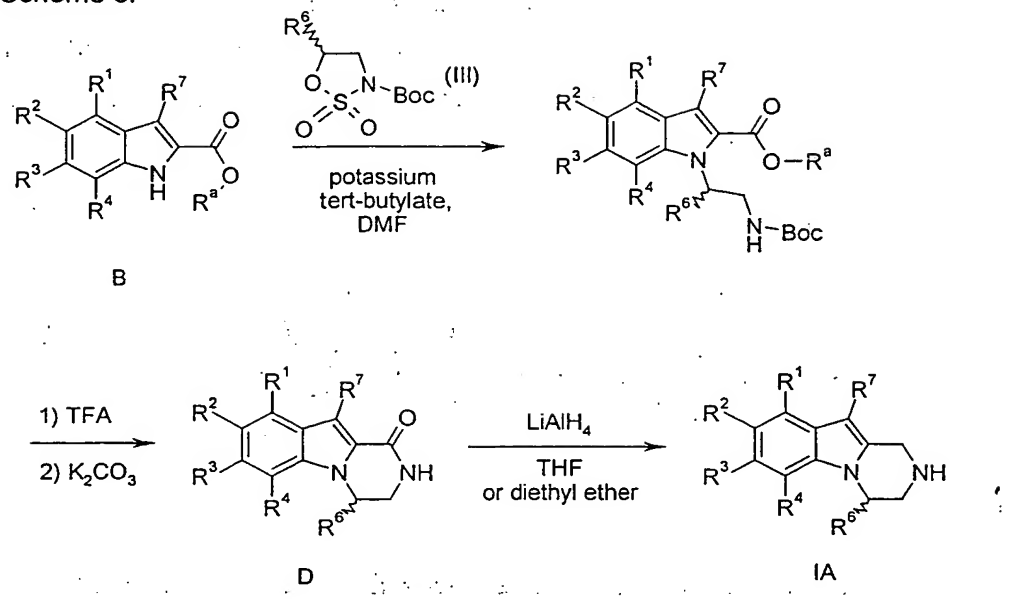
Scheme 2:



B C IA

Tetrahydro-pyrazinoindoles of formula IA can be prepared by a process where the indole-2-carboxylate of formula B is first reacted with an alpha halo alkanenitrile (e.g., 2-bromo propionitrile) in a suitable solvent (e.g., DMF) with a suitable base (e.g., NaH). The intermediate C is reduced and cyclized to the tetrahydro-pyrazinoindole IA by reaction with a suitable reducing agent in a suitable solvent (e.g., $LiAlH_4$ in THF or diethylether). R^b in Scheme 2 is an alkyl group, preferably a lower alkyl group, preferably methyl or ethyl.

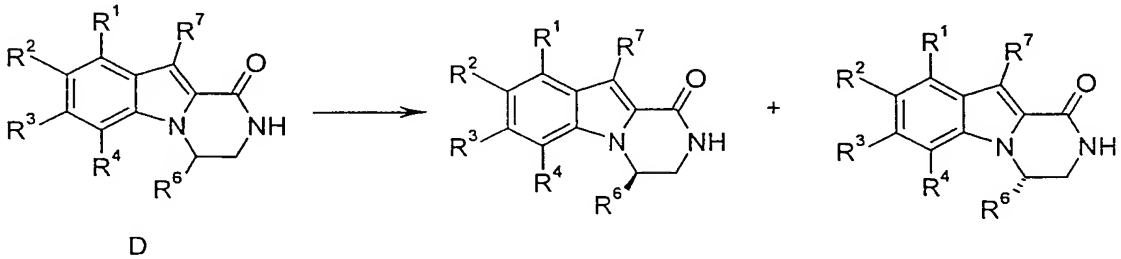
Scheme 3:



Tetrahydro-pyrazinoindoles of formula IA can also be prepared by a process where the indole-2-carboxylate of formula B is first reacted with the hitherto unknown Boc-sulfamidate (III) in a suitable solvent (e.g., DMF) with a suitable base (e.g., potassium tert-butylate or sodium hydride) followed by removal of the Boc protecting group and ring closure in the presence of base (e.g., potassium carbonate). The stereochemistry of the carbon atom attached to R^6 in Boc-sulfamidate III is inverted (>90% e.e.) in this reaction sequence. The intermediate amide (D) is reduced with a suitable reducing agent in a suitable solvent (e.g., $LiAlH_4$ in diethyl ether or borane-dimethylsulfide complex in THF). R^a in Scheme 3 is an alkyl group, preferably a lower alkyl group, preferably methyl or ethyl.

If racemic Boc-sulfamidate III is used in this process, the enantiomers of intermediate D can be obtained, e. g., by preparative chiral HPLC as depicted in Scheme 4.

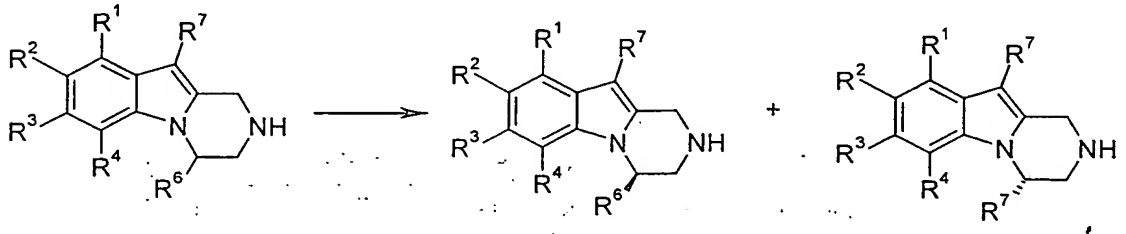
Scheme 4:



The enantiomers of tetrahydro-pyrazinoindoles IA can be obtained either by using a chiral sulfamidate (III) or by separation of the enantiomers by preparative chiral HPLC or

by crystallisation with suitable chiral acids, separation of the diastereomeric salts and isolation of the enantiomers from these salts. An alternative access to the enantiomers of pyrazinoindoles IA involves the separation of the enantiomers of the precursor C, e. g., by preparative chiral HPLC.

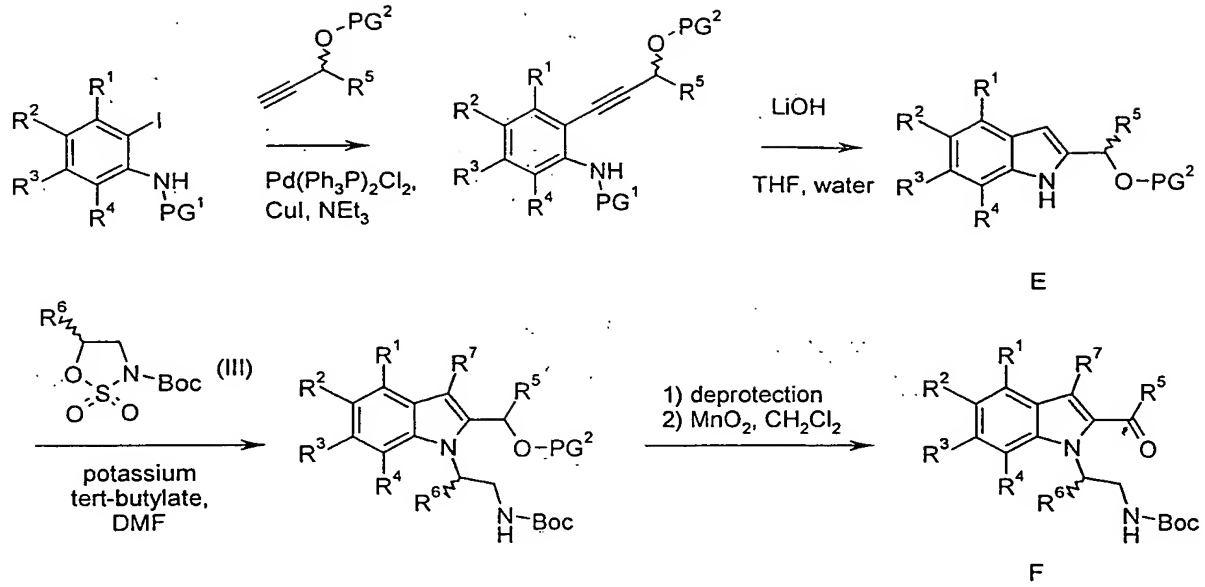
Scheme 5



IA

Indole derivatives F can be prepared according to scheme 6, starting from protected o-iodoanilines (a suitable protective group, PG^1, is, e.g. N-methoxycarbonyl) by cross-coupling reaction with suitably substituted and optionally protected carbinols (preferred protective groups are silyl ethers, especially preferred is tert-butyl-dimethylsilyl). The reaction proceeds in the presence of a suitable catalyst (e.g., bis-triphenylphosphine palladium dichloride and copper(I)iodide as co-catalyst) in a suitable solvent (e.g. triethylamine). The intermediate is treated with a base (e.g. LiOH in THF/water) to yield the indole derivative E.

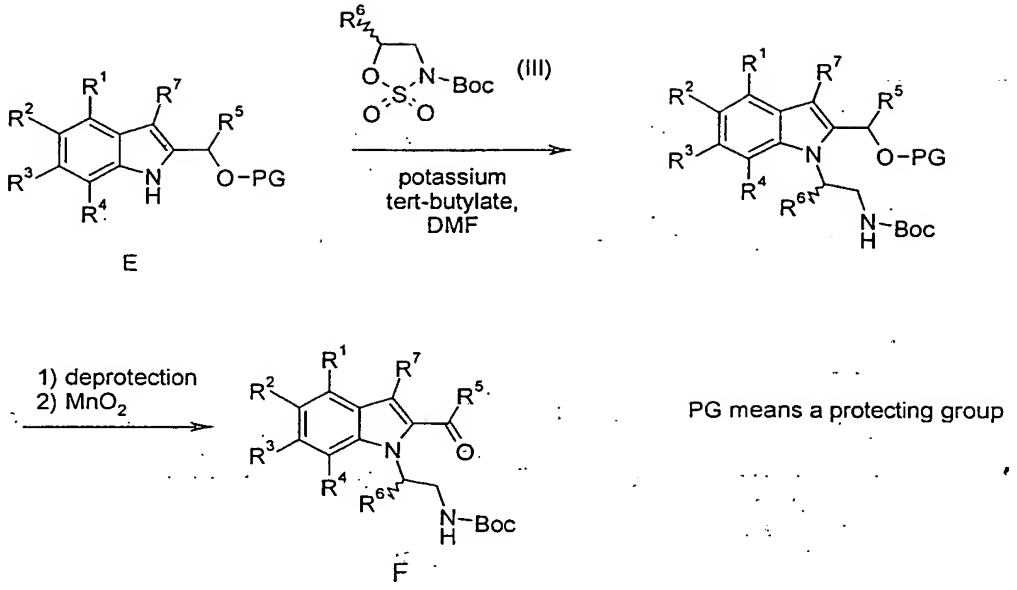
Scheme 6:



PG¹ and PG² are protecting groups

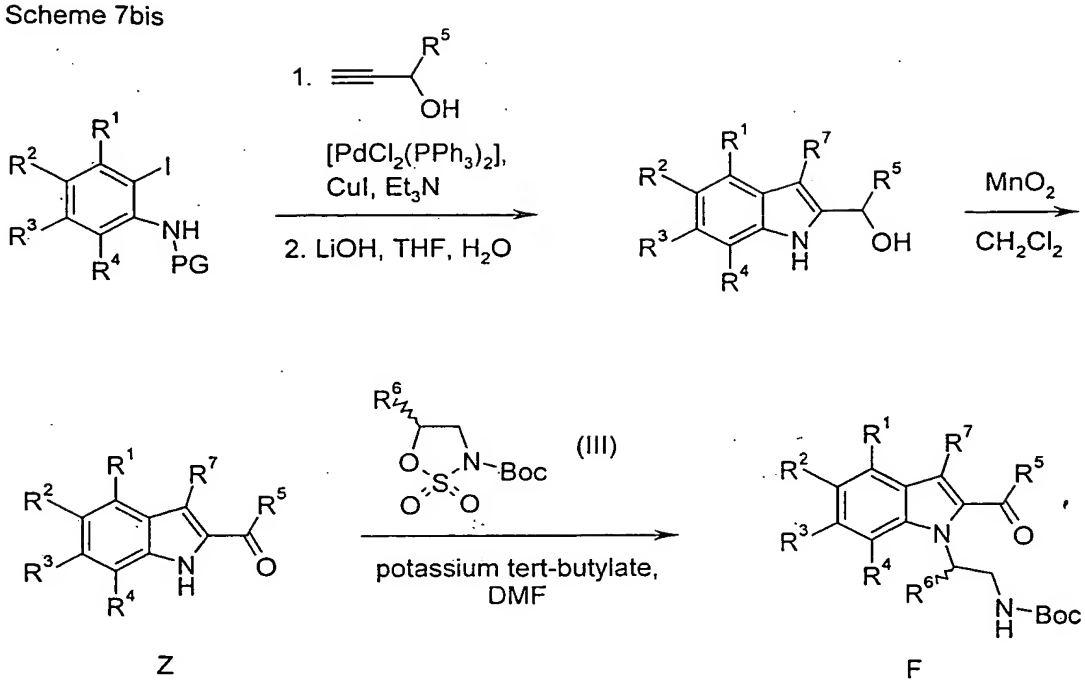
Alkylation of E with the hitherto unknown Boc-sulfamidate (III) in a suitable solvent (e.g., DMF) in the presence of a suitable base (e.g., NaH or potassium tert-butylate), followed by deprotection of the alcohol (e.g., with tetrabutylammoniumfluoride) in a solvent (e.g., THF) and oxidation of the alcohol (e. g., with manganese dioxide in dichloromethane) leads to intermediate F. The stereochemistry of the carbon atom attached to R^6 in Boc-sulfamidate III is inverted (>90% e.e.) in this reaction sequence.

Scheme 7:



Indole derivatives F can also be prepared according to scheme 7bis, starting from protected o-iodoanilines (a suitable protective group, PG^1, is, N-methoxycarbonyl) by cross-coupling reaction with propargyl alcohol derivatives in the presence of a suitable catalyst (e.g., bis-triphenylphosphine palladium dichloride and copper(I)iodide as co-catalyst) in a suitable solvent (e.g. triethylamine), followed by treatment with a base (e.g. LiOH in THF/water). The alcohol intermediate is oxidised, e. g., with manganese dioxide, to yield the indole derivative Z. Alkylation of Z with Boc-sulfamidate (III) in a suitable solvent (e.g., DMF) with a suitable base (e.g., potassium tert-butylate or NaH) leads to intermediate F. The stereochemistry of the carbon atom attached to R^6 in Boc-sulfamidate III is inverted (>90% e.e.) in this reaction.

Scheme 7bis

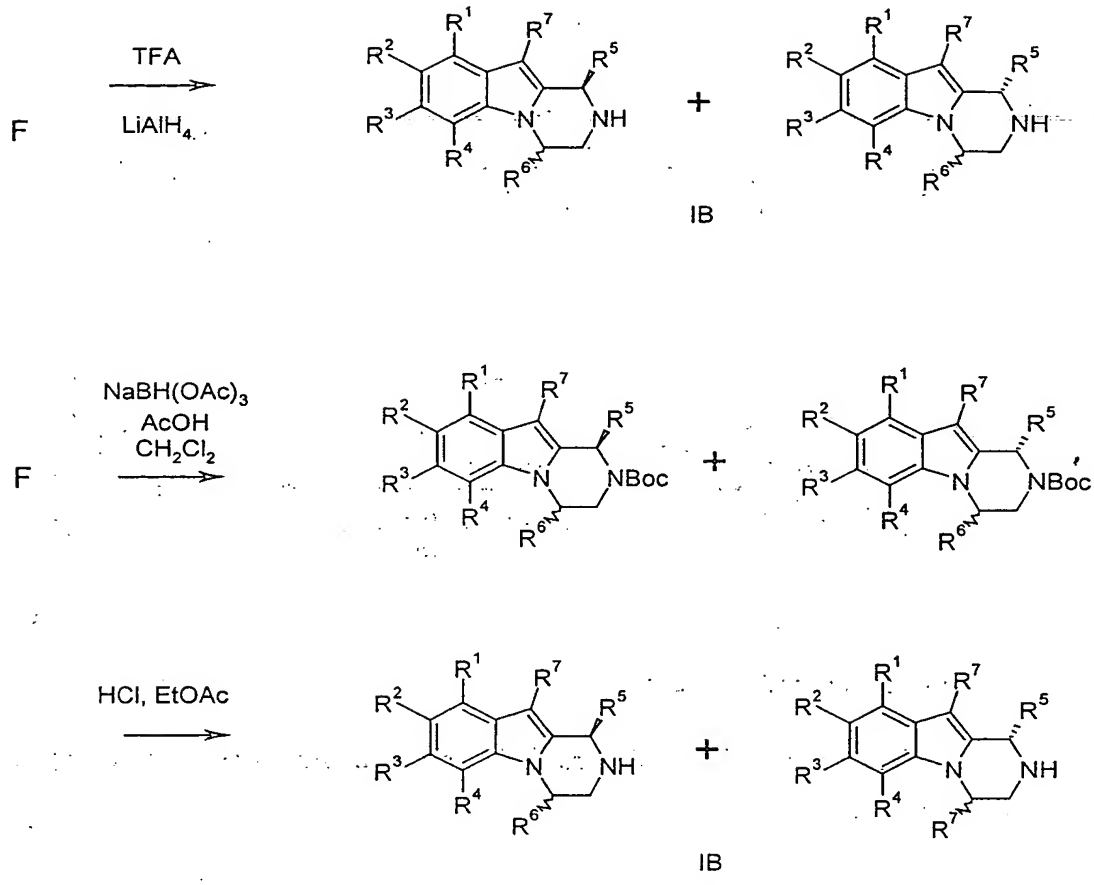


PG is a protective group

These intermediates of formula F can be further processed to compounds of formula IB by either

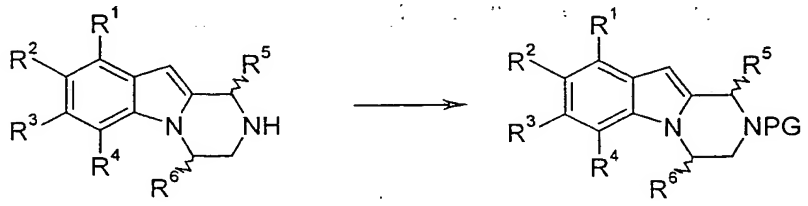
- removal of the Boc protecting group (e. g., with trifluoroacetic acid) to yield an imine intermediate which is not isolated but reduced directly with lithium aluminium hydride to yield IB as a separable mixture of epimers,
- or direct reductive amination (e.g., with sodium triacetoxyborohydride, molecular sieves and acetic acid in a suitable solvent, e.g., dichloromethane) followed by removal of the protecting group (e.g., with hydrochloric acid in ethyl acetate) as depicted in scheme 8.

Scheme 8



A variety of substituents R^7, preferably those functional groups that do not tolerate the methods described for the pyrazinoindole synthesis can be introduced starting from pyrazinoindole IC. To that end, the amine nitrogen of IC is protected, e. g., as the tert-butyl carbamate (protecting group PG) to generate compound G.

Scheme 9



Several examples for the elaboration of compound G are highlighted in Schemes 10 and 11 (other substituents, R^7, can be introduced using methods known in the art (e.g., A.

R. Katritzky et al. (eds.), 'Indoles' (Best Synthetic Methods), Academic Press, London, 1996, pp. 105-134):

a) Vilsmeier reaction (DMF-$POCl_3$) yields aldehyde H, which can be further converted, e. g., into

a1) alcohol derivative J (by reduction, e. g. with $NaBH_4$), which can be alkylated with a compound, R^{20}-X, to produce K (R^{20} is alkyl, cycloalkyl, and X is a leaving group, preferably Br or I);

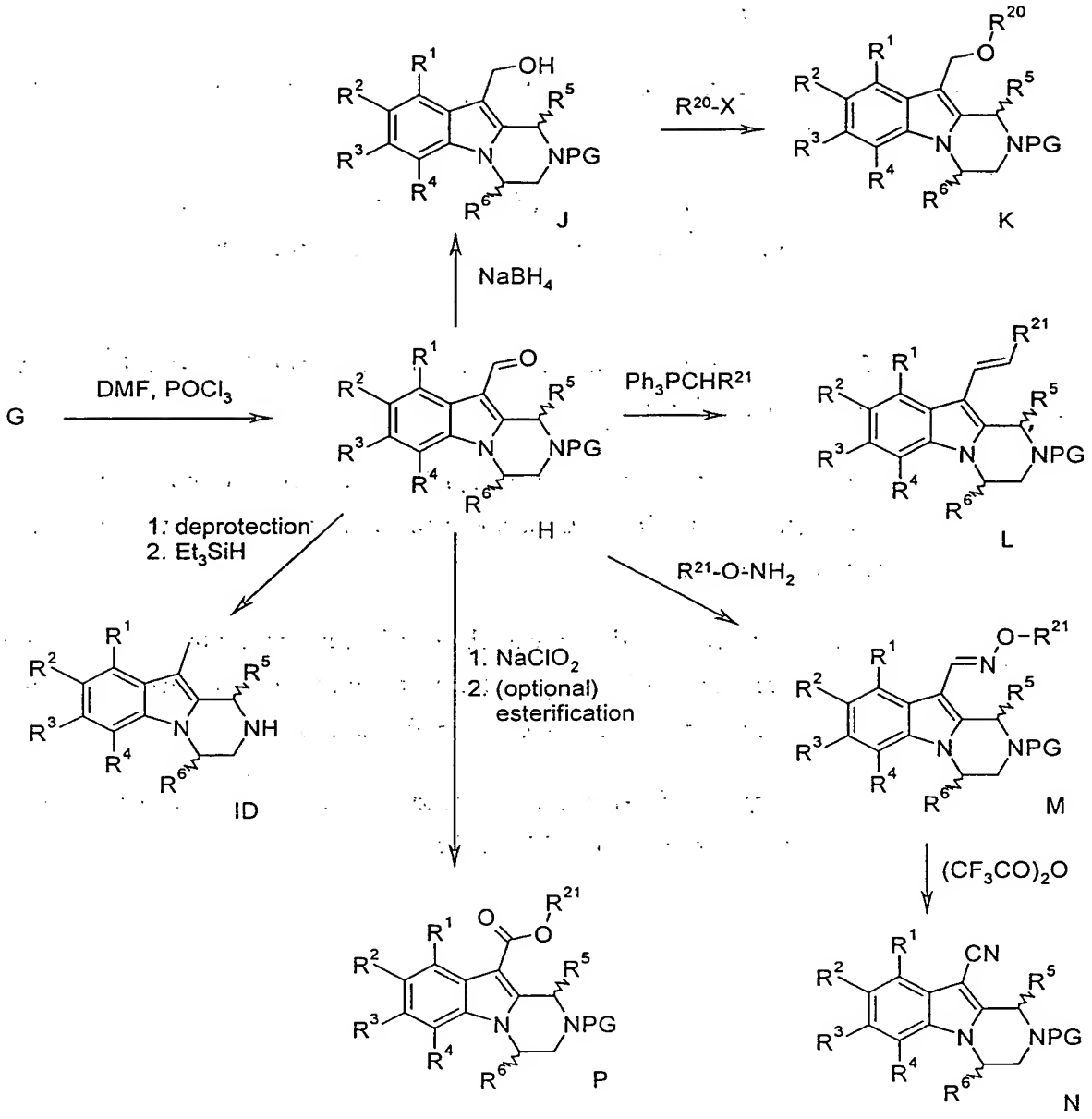
a2) olefin L (by e.g., treatment with a phosphorane, $Ph_3P{=}CHR^{21}$), where R^{21} is H, alkyl, cycloalkyl, alkenyl, aryl);

a3) 10-methyl-tetrahydropyrazino[1,2-a]indole ID (by deprotection, e. g., with hydrogen chloride in ethyl acetate in the case of PG = Boc, followed by reduction, e. g., with triethylsilane);

a4) hydroxyimino and oxime M (by condensation with hydroxylamine or a hydroxylamine-O-ether respectively), which can be transformed into nitrile N, e. g., by treatment with trifluoroacetic anhydride; and

a5) carboxylic acid derivative P by oxidation e.g. with sodium chlorite, optionally followed by esterification with alcohols, $R^{21}OH$.

Scheme 10



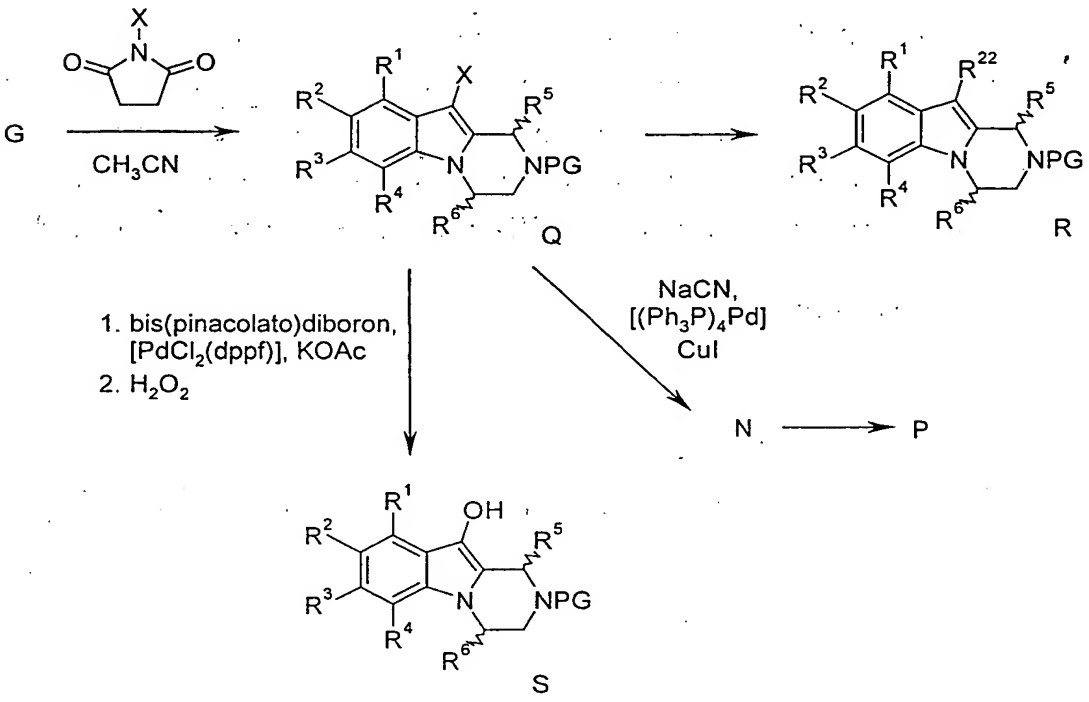
b) Halogenation (preferably with N-iodosuccinimide or N-bromosuccinimide in acetonitrile) yields halide Q, which can be further converted, e. g., into

b1) compound R, by cross-coupling reaction (R^{22} = alkyl, aryl, alkenyl, alkynyl) using methods known in the art (e. g., F. Diederich, P. J. Stang (eds.), Metal-catalysed Cross-coupling Reactions, Wiley-VCH, 1998);

b2) nitrile N, by reaction, e. g., with NaCN in the presence of $[(Ph_3P)_4Pd]$ and CuI in acetonitrile), which can be elaborated, e. g., into carboxylic acid derivative, P; and

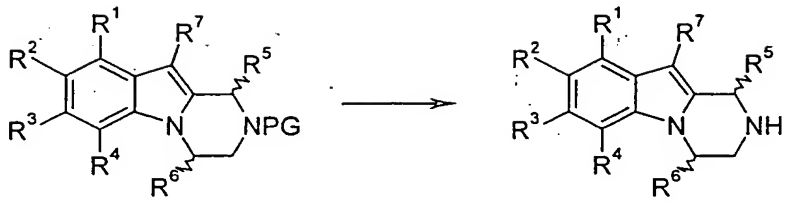
b3) compound S, e. g., by cross-coupling reaction with bis(pinacolato)diboron in the presence of a palladium catalyst, e. g., $[PdCl_2(dppf)]$, and a base, e. g., potassium acetate, followed by oxidation of the boronic acid intermediate with hydrogen peroxide.

Scheme 11



Cleavage of the protective group in compounds H, J, K, L, M, N, P, Q, R, or S (e. g., with acid such as trifluoroacetic acid or hydrogen chloride in a suitable solvent such as ethyl acetate in the case of PG = Boc) yields tetrahydropyrazino[1,2-a]indoles IB.

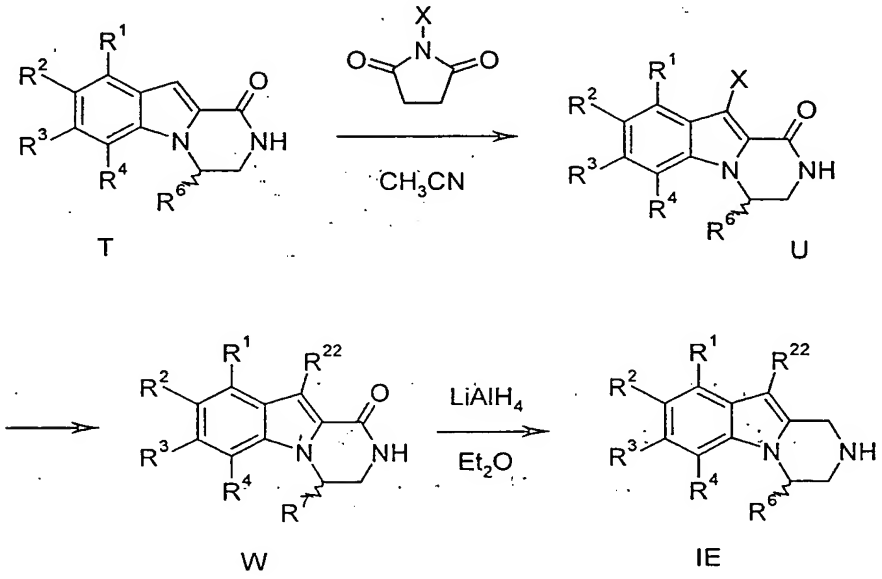
Scheme 12



H, J,..., S IB

Tetrahydropyrazino[1,2-a]indoles of formula IE can also be prepared as shown in Scheme 13. Amide T is halogenated (preferably with N-iodosuccinimide or N-bromosuccinimide in acetonitrile) to produce compound U, which is subjected to a cross-coupling reaction using methods known in the art (e. g., F. Diederich, P. J. Stang (eds.), Metal-catalyzed Cross-coupling Reactions, Wiley-VCH, 1988). Reduction of the cross-coupling product W (e. g., with $LiAlH_4$ in Et_2O) yields IE with R^{22} defined as before.

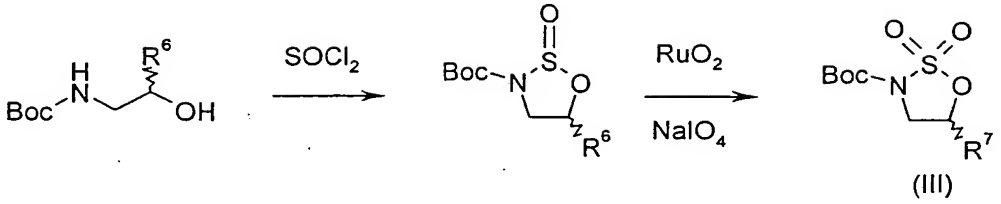
Scheme 13



T U W IE

Functional groups R^1 to R^4 that do not tolerate the methods described for the pyrazino-indole synthesis can be prepared from such functional groups that do by methods known in the art (e.g. March, Advanced Organic Chemistry 4th edition or Comprehensive Organic Functional Group Transformations, 1995).

Scheme 14:

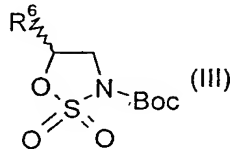


(III)

The hitherto unknown Boc-sulfamidate III can be prepared according to scheme 14 by treating Boc-protected ethanolamine derivatives with thionylchloride in a suitable solvent e.g. THF or ethyl acetate in the presence of a suitable base e.g. triethylamine or imidazole and oxidising the intermediate (e.g., with sodium metaperiodate and ruthenium(IV)oxide) in a suitable solvent (e.g., ethyl acetate). The stereochemistry of the carbon atom attached to R^6 remains unchanged (e.e. >97%) over this sequence.

The processes as described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

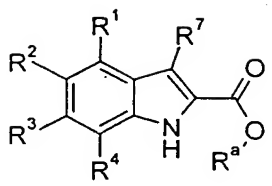
Another embodiment of the present invention relates to processes for the prepartion of compounds of formula (I) comprising comprising a reaction with a compound of formula (III)



(III)

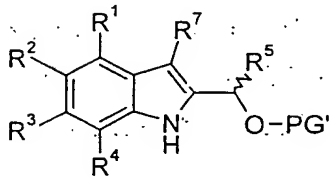
wherein R^6 is as defined above with a compound selected from the group consisting of

a)



wherein R^1, R^2, R^3, R^4, and R^7 are as defined above and R^a is alkyl; and

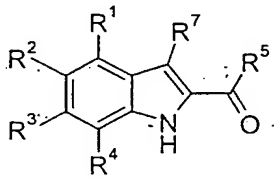
b)



E

wherein R^1, R^2, R^3, R^4, R^5, and R^7 are as defined above; and PG' is hydrogen or an OH-protecting group, e.g. trimethylsilyl, tert-butyldimethylsilyl, acetyl, methoxymethyl or2-tetrahydropyranyl.

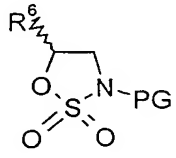
c)



Z

wherein R^1, R^2, R^3, R^4, R^5, and R^7 are as defined above;

Another preferred aspect of this invention are the intermediates of formula (III)



(III)

wherein R^6 is as defined abov e and PG is a nitrogen protecting group, e.g. BOC. Especially preferred embodiments of formula (III) are (S)-5-Methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester and (R,S)-5-Ethyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus, type II diabetes; and sleep apnea.

A further aspect of the invention is a compound according to formula I for use as therapeutically active substance.

According to another aspect of the present invention, there is provided the use of a compound of formula (I) in the manufacture of a medicament comprising a compound according to formula I for the treatment of disorders of the central nervous system, damage to the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, type II diabetes, and sleep apnoea.

According to a preferred aspect of this invention the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

According to a preferred aspect of this invention the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases, particularly wherein the toxic or infective CNS disease is encephalitis or meningitis.

A further preferred embodiment of the present invention is the above mentioned use, wherein the cardiovascular disorder is thrombosis.

Also preferred is the mentioned use of the compounds according to formula I, wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility.

Particularly preferred is the use of a compound of formula I in the manufacture of a medicament comprising a compound of formula I for the treatment of obesity.

Further preferred is a method of treatment of any of the above mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). Also preferred is the use or method as mentioned before, wherein said treatment is prophylactic treatment.

According to a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention there is provided a method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a compound according to formula I and a therapeutically effective amount of a lipase inhibitor, particularly preferred, wherein

the lipase inhibitor is orlistat. Also subject of the present invention is the mentioned method, wherein the administration is simultaneous, separate or sequential.

A further preferred embodiment of the present invention is the use of a compound of the formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor, particularly preferred, wherein the lipase inhibitor is orlistat.

Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Orlistat can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryl sulfate, Brij 96, or Tween 80; disintegrants like sodium starch glycolate, maize starch or derivatives thereof; polymers like povidone, crospovidone; talc; stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art. Preferably, orlistat is administered according to the formulation shown in the Examples and in U.S. Patent No. 6,004,996, respectively.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active

compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

ASSAY PROCEDURES

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2C} receptor the 5-HT_{2C} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2C} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, 118, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, 342, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, 9, 3482-90.

The thus determined activity of the compound of the Example is shown in Table 1.

Table 1

Compound	Method (a) Ki (2C)	Method (b) Ki (2B)	Method (c) Ki (2A)
Example 1	5.0 nM	86 nM	205 nM
Example 20	2.8 nM	44 nM	23 nM

Preferred compounds of formula I as described above have Ki (2C) values below 10000 nM; especially preferred compounds have Ki (2C) values below 1000 nM, particularly preferred compounds have Ki (2C) values below 100 nM. Most preferred compounds have Ki (2C) values below 30nM.

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx. 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

Table 2

Compound	h5-HT_{2c} EC_{50} (nM) Relative Efficacy (%)	h5-HT_{2A} EC_{50} (nM) Relative Efficacy (%)	h5-HT_{2B} EC_{50} (nM) Relative Efficacy (%)
Example 1	22 nM (83%)	640 nM (23%)	6.7 nM (53%)
Example 20	7 nM (91%)	163 nM (49%)	30 nM (26%)
Example 21	5 nM (80%)	121 nM (76%)	20 nM (40%)
Example 14	0.4 nM (88%)	536 nM (34%)	162 nM (38%)

The compounds of formula (I) have activity at the h5-HT2c receptor in the range of 10,000 to 0.1 nM.

Preferred compounds of formula I as described above have activity at the h5-HT2c receptor below 10000nM; especially preferred compounds below 1000nM, particularly preferred compounds below 100nM. Most preferred compounds have activity at the h5-HT2c receptor below 30nM.

EXAMPLES

Example 1

a) (R)-6-Ethyl-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

Lithium aluminium hydride (532 mg) was added in portions to a solution of (R)-6-ethyl-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one (800 mg, 3.50 mmol) in tetrahydrofuran (30 mL) and the resulting suspension was heated to reflux for 1 h. After cooling the reaction was quenched by careful addition of 1 M aqueous sodium potassium tartrate solution (50 mL). Then methanol (50 mL) and ethyl acetate (50 mL) were added, the organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to yield the title compound (750 mg, 100%). White solid. ISP-MS: m/e = 215.3 ($[M + H]^+$).

Intermediates:

b) (R)-6-Ethyl-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

Potassium tert-butylate (2.17 g, 19.3 mmol) was added to a solution of 7-ethyl-1H-indole-2-carboxylic acid ethyl ester (4.00 g, 18.4 mmol) in N,N-dimethylformamide (100 mL) at 0°C, then after 1 h (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (4.81 g, 20.2 mmol) was added and the solution was allowed to reach room temperature over 16 h. The solution was partitioned between 1 M aq. HCl solution (100 mL) and hexane/ethyl acetate 1:1 (200 mL). The organic layer was washed with sat. aq. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in dichloromethane (80 mL) and treated with trifluoroacetic acid (20 mL) at 0°C. After removal of the ice bath, the solution was stirred for 30 min, then evaporated under reduced pressure. The residue was dissolved in methanol (100 mL), then after addition of K_2CO_3 (25.4 g, 184 mmol) the mixture was stirred for 16 h at room temperature. Then water (200 mL) and ethyl acetate (200 mL) were added, the organic layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. Chromatography (70 g SiO_2, hexane/ethyl acetate gradient) yielded a foam which was precipitated with hexane to produce the title compound (1.20 g, 29%). White solid. EI-MS: m/e = 228.3 (M^+). The optical purity was determined by gas chromatography, using a chiral BGB-176-SE column (15 m x 0.25 mm), to be 96.2% e.e.

c) 7-Ethyl-indole-1-carboxylic acid tert-butyl ester

7-Ethylindole (106.0 g, 0.73 mol) was dissolved in acetonitrile (1 l) and di-tert-butyl dicarbonate (191.0 g, 0.87 mol) and 4-(dimethylamino)pyridine (4.43 g, 36.0 mmol) were added successively. After 4.5 h the reaction mixture was concentrated and the residue was purified by column chromatography over silica gel (0.032 – 0.060 mm) with n-hexane/tert-butyl methyl ether (9/1) as eluant to yield the desired product as colourless oil (179 g, 100%). EI-MS: m/e = 245.2 ([M])

d) 7-Ethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

2,2,6,6-Tetramethylpiperidine (2.21 g, 15.6 mmol) was dissolved in 30 mL tetrahydrofuran and cooled down to –75°C. n-Butyllithium (9 mL, 14.3 mmol, 1.6M solution in n-hexane) was added while maintaining the temperature below –70°C. After 50 min., a solution of 3.2 g (13.0 mmol) 7-ethyl-indole-1-carboxylic acid tert-butyl ester in 15 mL tetrahydrofuran was added and the temperature again kept below -70°C. After 50 min., ethyl chloroformate (1.4 mL (14.3 mmol) was added and the temperature was allowed to rise to –50°C. After 1 h the reaction mixture was poured into 30 mL saturated aq. ammonium chloride solution and the phases separated. The aqueous phase was extracted once with 50 mL diethyl ether and the combined organic extractions were washed successively with saturated aq. ammonium chloride solution and water, dried over magnesium sulfate, filtered and evaporated. The crude reaction product was flash-chromatographed over silica gel (0.030 – 0.060 mm) with n-hexane/tert-butyl methyl ether (39/1) as eluant to give the product as a yellow oil (2.3 g, 56.2%). EI-MS: m/e = 317.2 ([M])

e) 7-Ethyl-1H-indole-2-carboxylic acid ethyl ester

7-Ethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (76.6 g, 0.24 mol) was dissolved in 450 mL dichloromethane and cooled to 0°C. Trifluoroacetic acid (150.0 mL, 1.96 mol) was added within 30 min. and after an additional 45 min. the reaction mixture was concentrated at a rotary evaporator. The residue was dissolved in 300 mL dichloromethane and poured cautiously onto 500 mL saturated aq. sodium bicarbonate solution. The phases were separated and the aqueous phase was extracted twice with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. The residue was suspended in 400 mL n-hexane and put in an ultrasonic bath for 15 min. The suspension

was filtered and the filter cake was washed with 100 mL n-hexane. This procedure was repeated to give the desired product as a light brown solid (40.2 g, 76.6%). EI-MS: m/e = 217.1 ([M])

f) (S)-5-Methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester

To a solution of 11.15 g (S)-Carbamic acid, (2-hydroxypropyl)-, 1,1-dimethylethyl ester, in 100 mL tetrahydrofuran was added at –78°C 80 mL of a 1.6 M solution of n-butyllithium in n-hexane during 15 min. The resulting mixture was warmed to –15°C and stirred for 45 min. A solution of 7.5g thionyl chloride in 50 mL tetrahydrofuran was added during 5 min. The mixture was then warmed to –15°C and stirred for 90 min. The reaction mixture was partitioned between ethyl acetate and 10 % citric acid. The phases were separated and the organic phase was washed with sodium bicarbonate and brine, dried over magnesium sulfate, evaporated and purified by chromatography on silica gel with 3 : 1 hexane : ethyl acetate . The intermediate sulfamidite was taken up in 60 mL ethyl acetate and 100 mL of a 10% solution of sodium metaperiodate was added. The mixture was cooled to 0°C and 0.21 g ruthenium dioxide dihydrate was added and the mixture was stirred at this temperature for 45 min. The phases were separated and the organic phase was purified by chromatography on silica gel with 2 : 1 hexane : ethyl acetate to yield 5.3g of the title compound as white crystals after recrystallisation from ethanol (m.p.:111.6-115°C). $\alpha_D^{20} = +37.1$

Example 2

a) (R)-4-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound, ISP-MS: m/e = 255.1 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (R)-4-methyl-7-trifluoromethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellowish solid, m.p. 123-125°C.

Intermediate:

b) (R)-4-Methyl-7-trifluoromethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

The title compound (EI-MS: m/e = 268.2 (M^+)) was produced in accordance with the general method of example 1b) from 6-trifluoromethyl-1H-indole-2-carboxylic acid

ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. White solid, m.p. 201-204°C.

Example 3

a) (R)-7-Bromo-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound, ISP-MS: m/e = 265.2, 267.2 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (R)-7-bromo-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Colourless amorphous solid.

Intermediate:

b) (R)-7-Bromo-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

The title compound (EI-MS: m/e = 279.1, 281.1 (M^+)) was produced in accordance with the general method of example 1b) from 6-bromo-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless amorphous solid.

Example 4

a) (R)-9-Chloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride

The title compound, ISP-MS: m/e = 221.2 ($[M + H - Cl]^+$), was produced in accordance with the general method of example 1a) from (R)-9-chloro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one and crystallised as HCl salt. Colourless solid, m.p. 234-237 °C dec.

Intermediate:

b) (R)-9-Chloro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

The title compound (EI-MS: m/e = 234.1 (M^+)) was produced in accordance with the general method of example 1b) from 4-chloro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid, m.p. 180-184°C.

Example 5

a) (R)-7-Chloro-8-fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole.

The title compound, ISP-MS: m/e = 239.2 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (R)-7-chloro-8-fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Colourless amorphous solid.

Intermediate:

b) (R)-7-Chloro-8-fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

The title compound (EI-MS: m/e = 253.1 (M^+)) was produced in accordance with the general method of example 1b) from 6-chloro-5-fluoro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid, m.p. >250°C.

Example 6

a) (R)-4,8-Dimethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride

The title compound, ISP-MS: m/e = 269.3 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (R)-4,8-dimethyl-7-trifluoromethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

Intermediates:

b) (R)-4,8-Dimethyl-7-trifluoromethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (EI-MS: m/e = 253.1 (M^+)) was produced in accordance with the general method of example 1b) from 5-methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid, m.p. >250°C.

c) 5-Methyl-6-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester

The title compound (EI-MS: m/e = 271.1 (M^+)) was produced in accordance with the general method of example 1c to 12e) from 5-methyl-6-trifluoromethyl-1H-indole. Colourless solid, m.p. 176-178°C.

Example 7

a) (R)-7,9-Dichloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride

The title compound (ISP-MS: m/e = 255.1 ([M+H^+])) was produced in accordance with the general method of example 1a) from (R)-7,9-dichloro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one and was crystallised as HCl salt. Colourless amorphous solid???

Intermediate:

b) (R)-7,9-Dichloro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 269.2 ([M+H^+])) was produced in accordance with the general method of example 1b) from 4,6-dichloro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid.

Example 8

a) (R)-6,9-Difluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride

The title compound (ISP-MS: m/e = 223.2 ([M+H^+])) was produced in accordance with the general method of example 1a) from (R)-6,9-difluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one and was crystallised as HCl salt. Colourless amorphous solid????.

Intermediate

b) (R)-6,9-Difluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 237.1 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 4,7-difluoro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid.

Example 9

a) (R)-6-Fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 205.2 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-6-fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellow oil.

Intermediate

b) (R)-6-Fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 219.2 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 7-fluoro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid.

Example 10

a) (R)-4,6-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 201.2 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-4,6-dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellow oil.

Intermediate

b) (R)-4,6-Dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 215.3 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 7-methyl-1H-indole-2-carboxylic acid ethyl

ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless oil.

Example 11

a) (R)-8-Fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 205.2 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-8-fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellow oil.

Intermediate

b) (R)-8-Fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 219.2 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 5-fluoro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid.

Example 12

a) (R)-7-Bromo-9-fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 285.0 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-7-bromo-9-fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Colourless solid.

Intermediate

b) (R)-7-Bromo-9-fluoro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 297.2 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 6-bromo-4-fluoro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Colourless solid.

Example 13

a) (R)-7-Chloro-10-methoxy-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound, ISP-MS: m/e = 251.2 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (R)-7-chloro-10-methoxy-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellow oil.

Intermediate

b) (R)-7-Chloro-10-methoxy-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (EI-MS: m/e = 264.1 (M^+)) was produced in accordance with the general method of example 1b) from 6-chloro-3-methoxy-1H-indole-2-carboxylic acid ethyl ester (EP-572863) and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. White solid.

Example 14

a) (R)-7-Chloro-4,6,10-trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole oxalate

Lithium aluminium hydride (64 mg, 1.67 mmol) was added in portions to a solution of (R)-7-chloro-4,6,10-trimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one (200 mg, 0.76 mmol) and the resulting suspension was heated to reflux for 5 h. After cooling the reaction was quenched by careful addition of 1 M aqueous sodium potassium tartrate solution (20 mL). Then ether (20 mL) was added, the organic layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in ether (3 mL) and treated with a solution of oxalic acid (200 mg, 2.22 mmol) in ethanol (1 mL). The precipitate was collected by filtration and dried to yield the title compound (116 mg, 45%). Off-white solid. ISP-MS: m/e = 249.2 ($[M + H - C_2H_2O_4]^+$). Anal. calc. for $C_{16}H_{19}ClN_2O_4$ (338.79): C 56.72, H 5.65, N 8.27; found: C 56.64, H 5.41, N 8.22.

Intermediate

b) (R)-7-Chloro-4,6,10-trimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (EI-MS: m/e = 262.1 (M^+)) was produced in accordance with the general method of example 1b) from 6-chloro-3,7-dimethyl-1H-indole-2-carboxylic

acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. White solid.

Example 15

a) (RS)-7-Bromo-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound, ISP-MS: m/e = 279.1, 281.2 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (RS)-7-bromo-4-ethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Colourless oil.

Intermediate

b) (RS)-7-Bromo-4-ethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 293.2, 295.2 ($[M + H]^+$)) was produced in accordance with the general method of example 1b) from 6-bromo-1H-indole-2-carboxylic acid ethyl ester and (RS)-5-ethyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. White solid.

Example 16

a) (R)-7-Bromo-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole.

(RS)-7-Bromo-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole (230 mg, 0.82 mmol) was subjected to chromatographic separation using a Chiralcel® OD-H column and heptane/2-propanol 95:5 as the eluant. This yielded the title compound (89 mg, 39%; colourless oil; EI-MS: m/e = 278.1 (M^+); α_D^{20}: -65.8° (c = 0.25, CH_2Cl_2). and its enantiomer (S)-7-bromo-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole (89 mg, 39%). Colourless oil. α_D^{20}: +65.0° (c = 0.32, CH_2Cl_2),

Example 17

a) (R)-4-Methyl-6-trifluoromethoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

A solution of (R)- 4-methyl-6-trifluoromethoxy-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one (800 mg, 2.81 mmol) in tetrahydrofuran (4 mL) was added to a suspension of lithium aluminium hydride (420 mg, 11.1 mmol) in tetrahydrofuran (4 mL) and the resulting mixture was heated to reflux for 90 min. After cooling the reaction mixture was

slowly added to a cooled saturated aqueous sodium potassium tartrate solution. The resulting suspension was filtered on dicalite and the organics extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel (n-hexane/ethyl acetate to ethyl acetate/methanol gradient) to yield the title compound as a light yellow solid (385 mg, 51%). Mp: 58-60°C; EI-MS: m/e = 270.1 (M^+).

Intermediates:

b) (R)-4-Methyl-6-trifluoromethoxy-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

Sodium hydride (280mg of a 60% dispersion in mineral oil, 7mmol) was added to a solution of 7-trifluoromethoxy-1H-indole-2-carboxylic acid ethyl ester (1.53g, 5.6mmol) and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (1.53g, 6.45mmol) in N,N-dimethylformamide (15mL) at 0°C. The solution was allowed to reach room temperature and stirred 36 h. Further amounts of sodium hydride (56mg) and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (306mg) were added to complete the reaction. To the solution was added 10% aq. citric acid solution and the mixture stirred 1h at room temperature. The organics were extracted with ethyl acetate (2x), the combined organic phases washed with sat. aq. $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in dichloromethane (25mL), cooled to 0°C and treated with trifluoroacetic acid (12mL). After removal of the ice bath, the solution was stirred for 30 min and evaporated under reduced pressure. The residue was taken up in methanol (20mL) and K_2CO_3 (2.52g, 19.5mmol) added, and the mixture stirred 15h at room temperature. The mixture was filtered, the filtrate diluted with ethyl acetate, washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate gradient) to afford the product as a pale yellow foam (89mg, 64%). ISP-MS: m/e = 285.1 (M^++H).

c) 7-Trifluoromethoxy-1H-indole-2-carboxylic acid ethyl ester

The title compound (EI-MS: m/e = 273.1 (M^+)) was produced in accordance with the general method of example 1c to 12e) from 7-trifluoromethoxy-1H-indole. Light brown amorphous solid.

d) 7-Trifluoromethoxy-1H-indole

Potassium hydroxide (17.9 g, 321 mmol) was boiled for 2 h in *t*-butanol (500 mL). (2-Trifluoromethoxy-6-trimethylsilanylethynyl-phenyl)-carbamic acid ethyl ester (52.8 g, 153 mmol) dissolved in *t*-butanol (500 mL) was added and boiling was continued for 2h. The solvent was removed in vacuo and the residue was partitioned between diethyl ether and water. The organic phases were washed with brine, pooled and dried with $MgSO_4$. Evaporation of the solvent yielded 31.8 g of brownish oil, which was purified by chromatography on silica gel with hexane/ethylacetate (9:1). This yielded the title compound, (30.2 g, 98%) as a yellow oil. (EI-MS: m/e = 201.0 (M^+))

e) (2-Trifluoromethoxy-6-trimethylsilanylethynyl-phenyl)-carbamic acid ethyl ester

Bis(triphenylphosphine)palladium(II) dichloride (1.1 g, 1.6 mmol) and copper(I) iodide (0.3 g, 1.6 mmol) were added to triethylamine (600 mL) and heated with stirring for 20 min. The mixture was cooled to room temperature and (2-iodo-6-trifluoromethoxy-phenyl)-carbamic acid ethyl ester (60.2 g, 160 mmol) was added. After stirring for 30 min at room temperature trimethylsilylacetylene (21.1 g, 152 mmol) was added and the mixture was stirred for another 2h at room temperature. Triethylamine was removed in vacuo and the residue was partitioned between water and diethyl ether. The organic phases were washed with 1N HCl, brine, pooled and dried with $MgSO_4$. Evaporation of the solvent yielded 57 g of brownish solid, which was purified by chromatography on silica gel with hexane/ethyl acetate (9:1). This yielded the title compound, (52.8 g, 95%) as a beige amorphous solid. (EI-MS: m/e = 345.0 (M^+))

f) (2-Iodo-6-trifluoromethoxy-phenyl)-carbamic acid ethyl ester

(2-Trifluoromethoxy-phenyl)-carbamic acid ethyl ester (42.4 g, 0.17 mol) was dissolved in THF (800 mL) and cooled to –70°C. *sec*-BuLi in cyclohexane (280 mL, 1.3 M) was added dropwise at this temperature with stirring. Stirring was continued for 1 h after addition was complete. A solution of iodine (43.2 g, 0.17 mol) in THF (160 mL) was added dropwise at –70 °C. Stirring was continued for 1h after addition was complete and the mixture was hydrolysed with saturated ammonium chloride solution. Water was added and the mixture was extracted with diethyl ether. The organic phases were washed with 40% sodium bisulfite, water, brine, pooled and dried with $MgSO_4$. Evaporation of the solvent yielded the title compound, (60.2 g, 94%) as a colourless amorphous solid. (EI-MS: m/e = 374.9 (M^+))

g) (2-Trifluoromethoxy-phenyl)-carbamic acid ethyl ester

2-(Trifluoromethoxy)aniline (50 g, 0.282 mol) was dissolved in DME (1000 mL) and cooled to –5°C. Sodium hydride (12.3 g, 55%, 0.282 mol) was added in portions and the suspension was allowed to warm to room temperature. Ethyl chloroformate (23.5 mL, 0.245 mol) was added drop by drop and the mixture was stirred for 2 h at room temperature and for 1.5 h at reflux after addition was complete. Hydrolysis was with water (110 mL). The phases were separated and the water phase was extracted with ethyl acetate. The organic phases were washed with brine, pooled and dried with $MgSO_4$. Evaporation of the solvent yielded 70.6 g of brown oil, which was purified by chromatography on silica gel with hexane/ethyl acetate (6:1). This yielded the title compound, (44.2 g, 62%) as a beige yellow oil. (EI-MS: m/e = 249.1 (M^+)).

Example 18

a) (R)-7-Chloro-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 235.3 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-7-chloro-4-ethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.Yellowish oil.

Intermediate

b) (R)-7-Chloro-4-ethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 249.2 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 6-chloro-1H-indole-2-carboxylic acid ethyl ester and (RS)-5-ethyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester followed by a chromatographic separation of the enantiomers on a ChiralPak AD-column. Light brown solid.

Example 19

a) (R)-4-Methyl-7,9-bis-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 322.1 ([M$^+$])) was produced in accordance with the general method of example 1a) from (R)-4-methyl-7,9-bis-trifluoromethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellowish oil.

Intermediate

b) (R)-4-Methyl-7,9-bis-trifluoromethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 336.0([M^+])) was produced in accordance with the general method of example 1b) from 4,6-bis-trifluoromethyl-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester .

Example 20

a) (R)-7-Chloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 221.3 ([$M+H^+$])) was produced in accordance with the general method of example 1a) from (R)-7-chloro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellowish solid.

Intermediate

b) (R)-7-Chloro-4-methyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 235.2 ([$M+H^+$])) was produced in accordance with the general method of example 1b) from 6-chloro-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Off-white solid.

Example 21

a) (R)-4,6,9-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 215.4 ([$M+H^+$])) was produced in accordance with the general method of example 1a) from (R)-4,6,9-trimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellowish oil.

Intermediate

b) (R)-4,6,9-Trimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 229.2 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 4,7-dimethyl-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Yellowish foam.

Example 22

a) (R)-4,6,7-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 215.4 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-4,6,7-trimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.Yellowish solid.

Intermediate

b) (R)-4,6,7-Trimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 229.2 ([M+H$^+$])) was produced in accordance with the general method of example 1b) from 6,7-dimethyl-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Yellowish foam.

Example 23

a) (R)-7-Chloro-4,6-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 235.2 ([M+H$^+$])) was produced in accordance with the general method of example 1a) from (R)-7-chloro-4,6-dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellowish semisolid.

Intermediate

b) (R)-7-Chloro-4,6-dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 248.1 ([M$^+$])) was produced in accordance with the general method of example 1b) from 6-chloro-7-methyl-1H-indole-2-carboxylic acid

ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Yellowish semisolid.

Example 24

a) (R)-4,8-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 200.2 ([M^+])) was produced in accordance with the general method of example 1a) from (R)-4,8-dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Waxy solid.

Intermediate

b) (R)-4,8-Dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one

The title compound (ISP-MS: m/e = 214.2 ([M^+])) was produced in accordance with the general method of example 1b) from 5-methyl-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Waxy solid.

Example 25

a) (R)-8-Fluoro-1-methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 273.2 ([$M+H^+$])) was obtained by chiral chromatography on a ChiralPak AD-column of the racemic mixture. Light yellow solid.

Intermediate:

b) (RS)-8-Fluoro-1-methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (ISP-MS: m/e = 272.1 ([M^+])) was produced from [2-(2-acetyl-5-fluoro-6-trifluoromethyl-indol-1-yl)-ethyl]-carbamic acid tert-butyl ester as follows:

[2-(2-Acetyl-5-fluoro-6-trifluoromethyl-indol-1-yl)-ethyl]-carbamic acid tert-butyl ester (205 mg) was dissolved in methylene chloride (6 mL) and was treated at room temperature with trifluoroacetic acid (6 mL) for one hour. The reaction mixture was poured into aqueous NaOH and the pH was brought to 14. The mixture was extracted

three times with ethyl acetate, the organic phases were pooled, dried over sodium sulfate and the solvent was removed. The residue was taken up in ether (15 mL) and treated with lithium aluminium hydride (50 mg). The reaction was refluxed for three hours. The reaction mixture was poured in aqueous hydrochloric acid. The mixture was extracted three times with ethyl acetate, the organic phases were pooled, dried over sodium sulfate and the solvent was removed. The residue was chromatographed on silica gel (eluant: 95/5 methylene chloride/methanol). The title compound was obtained as a light yellow resin in 78% yield.

c) [2-(2-Acetyl-5-fluoro-6-trifluoromethyl-indol-1-yl)-ethyl]-carbamic acid tert-butyl ester

The title compound (ISP-MS: m/e = 272.1 ([M^+])) was produced from 2-[1-(tert-butyl-dimethyl-silanyloxy)-ethyl]-5-fluoro-6-trifluoromethyl-1H-indole as follows:

2-[1-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-5-fluoro-6-trifluoromethyl-1H-indole (1520 mg) was dissolved in tetrahydrofuran (30 mL) and was treated at 0°C with sodium hydride (275 mg; 50% in oil), after 30min, 2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (1410 mg) was added and the reaction was allowed to proceed overnight. The reaction mixture was poured into aqueous hydrochloric acid. The mixture was extracted three times with ethyl acetate, the organic phases were pooled, dried over sodium sulfate and the solvent was removed. The residue was chromatographed on silica gel (eluant: hexane/ethyl acetate 85/15). 1.47 g N-alkylated product (69% yield) was obtained.

This compound (1.43 g) was dissolved in tetrahydrofuran (20 mL) and was treated with N-tetrabutyl ammonium fluoride (3 equivalents) and stirred 5h. The reaction mixture was poured into brine. The mixture was extracted three times with ethylacetate, the organic phases were pooled, dried over sodium sulfate and the solvent was removed. The residue was chromatographed on silica gel (eluant: hexane/isopropanol 87/13). 1.04 g of deprotected compound (94% yield) was obtained.

This compound (250 mg) was dissolved in dichloromethane (8 mL) and was treated with manganese dioxide (15 equivalents) and stirred 18h. The reaction mixture was filtered through dicalite and the solvent was removed. The residue was chromatographed on silica-gel (eluant: hexane/ethyl acetate 65/35). 214 mg of the title-compound (86% yield) was obtained as a light yellow solid.

d) 2-[1-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-5-fluoro-6-trifluoromethyl-1H-indole

The title compound (ISP-MS: m/e = 361.2 ([M^+])) was produced from (4-fluoro-2-iodo-5-trifluoromethyl-phenyl)-carbamic acid methyl ester as follows:

(4-Fluoro-2-iodo-5-trifluoromethyl-phenyl)-carbamic acid methyl ester (1520 mg) was dissolved in triethylamine (20 mL). Bis-(triphenylphosphin)-palladium (II) dichloride (193 mg; 5 mol %), copper (I) iodide (52 mg; 5 mol%) and tert-butyl-dimethyl-(1-methyl-prop-2-ynyloxy)-silane (1.22 g; 1.2 equivalent) were added and under exclusion of oxygen the reaction mixture was heated 3h at 50°C. The reaction mixture was poured into chilled aqueous hydrochloric acid (25%) and extracted three times with ethyl acetate. The organic phases were pooled, dried over sodium sulfate and the solvent was removed. The residue was chromatographed on silica gel (eluant: hexanes/ ethyl acetate 95/5). 2.44 g of the {2-[3-(tert-butyl-dimethyl-silanyloxy)-but-1-ynyl]-4-fluoro-5-trifluoromethyl-phenyl}-carbamic acid methyl ester (quantitative yield) was obtained.

This compound (2.31 g) was dissolved in tetrahydrofuran (35 mL), treated with 2N aqueous lithium hydroxide (6 equivalents) and refluxed 4h. The reaction mixture was poured into brine. The mixture was extracted three times with ethyl acetate, the organic phases were pooled, dried over sodium sulfate and the solvent was removed. The residue was chromatographed on silica-gel (eluant: hexane/ ethyl acetate 95/5). The title compound (1.54 g; 77% yield) was obtained as a brown liquid.

Example 26

a) (R)-8-Bromo-4,7-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride

A solution of 0.12 g (R)-8-bromo-4,7-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester in 3 mL of a 2M solution of hydrochloric acid in ethyl acetate was stirred at room temperature under argon for 2h. The precipitate was collected by filtration and dried to constant weight to yield the title compound (0.065 g) as off-white crystals. m.p.: 241°C (dec.); MS: M+H=279.1; HNMR: (250 MHz, DMSO-d6, δ [ppm]) 1.50 (d, J=6.5Hz, 3H); 2.45 (s, 3H); 3.48-3.74 (m, 2H); 4.36-4.58 (m, 2H); 4.74-4.89 (m, 1H); 6.35 (s, 1H); 7.54 (s, 1H); 7.78(s, 1H).

Intermediates:

b) (R)-8-Bromo-4,7-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester

A mixture of 0.75 g (R)-(2-{5-bromo-2-[dimethyl-(1,1,2-trimethyl-propyl)-silanyloxymethyl]-6-methyl-indol-1-yl}-propyl)-carbamic acid tert-butyl ester and 0.52 g ammonium fluoride in 7.5 mL methanol was stirred 18h at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase was washed with 10% citric acid, 10% sodium bicarbonate and brine, dried over magnesium sulfate and evaporated to dryness. The residue was taken up in 6 mL dichloromethane and 0.59 g manganese dioxide was added. The mixture was stirred 2h at room temperature. The solids were removed by filtration over dicalite and the filtrate was evaporated to dryness. The residue was taken up in 5 mL dichloromethane and 0.072 mL acetic acid and 1.00 g molecular sieve (powder, 4Å) were added. To the resulting suspension was added 0.536 g sodium triacetoxyborohydride, and the mixture was stirred 1h at room temperature. Another 0.536 g sodium triacetoxyborohydride was added and the mixture was stirred 1h. The solids were removed by filtration over dicalite and the filtrate was purified by chromatography on silica gel with hexane : ethyl acetate = 2 : 1 to yield 0.295 g of the title compound as a yellow solid melting at 113-114°C after crystallisation from hexane.

c) (R)-(2-{5-Bromo-2-[dimethyl-(1,1,2-trimethyl-propyl)-silanyloxymethyl]-6-methyl-indol-1-yl}-propyl)-carbamic acid tert-butyl ester

To a solution of 0.95 g 5-bromo-2-[dimethyl-(1,1,2-trimethyl-propyl)-silanyloxymethyl]-6-methyl-1H-indole in 10 mL N,N-dimethylformamide was added 0.143 g sodium hydride 55-65% in oil and the mixture was stirred 30min at room temperature. To the resulting mixture was added (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester (0.703 g) and the mixture was stirred 2h at room temperature. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase was washed with 10% citric acid and brine, dried over magnesium sulfate and purified by chromatography on silica gel with hexane: ethyl acetate= 5 : 1 to yield 0.789 g of the title compound as a slightly yellow oil. MS: M+H=541.3

d) 5-Bromo-2-[dimethyl-(1,1,2-trimethyl-propyl)-silanyloxymethyl]-6-methyl-1H-indole

To a suspension of 0.5144 g lithium hydroxide in 37 mL dimethylsulfoxide and 3.7 mL water was added 1.800 g (4-bromo-2-{3-[dimethyl-(1,1,2-trimethyl-propyl)-silanyloxy]-prop-1-ynyl}-5-methyl-phenyl)-carbamic acid methyl ester and the mixture was heated 2h at 80°C. Water and ethyl acetate were added. The pH was adjusted to 6.0 by addition of hydrochloric acid. The phases were separated and the organic phase was washed with 10% sodium bicarbonate and brine and purified by chromatography on silica gel with hexane: ethyl acetate=9:1 to yield 0.97 g of the title compound as a colourless oil. MS: M=383.1

e) (4-Bromo-2-{3-[dimethyl-(1,1,2-trimethyl-propyl)-silanyloxy]-prop-1-ynyl}-5-methyl-phenyl)-carbamic acid methyl ester

To a solution of 3.70 g (4-bromo-2-iodo-5-methyl-phenyl)-carbamic acid methyl ester and 0.070 g bis-triphenylphosphine palladium dichloride and 0.038 g cuprous iodide in 25 mL triethylamine was added 2.38 g dimethyl (2-propynyloxy)(1,1,2-trimethylpropyl)- silane and the mixture was heated 2h at reflux. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase was washed with 1N hydrochloric acid, sodium bicarbonate and brine, dried with magnesium sulfate and purified by chromatography on silica gel with hexane: ethyl acetate=4:1 to yield 1.92 g of the title compound as a light brown oil. MS: $M+NH_4^+$=457.0 $M+Na^+$=462.2

f) (4-Bromo-2-iodo-5-methyl-phenyl)-carbamic acid methyl ester

To a solution of 5.00g (4-bromo-3-methyl-phenyl)-carbamic acid methyl ester in 50 mL acetonitrile were added at 0°C 4.84 g N-iodosuccinimide and 0.18 mL trifluoromethanesulfonic acid. The mixture was stirred 18h at room temperature. The solid was collected by filtration, washed with cold acetonitrile and dried to constant weight to yield 5.800 g of the title compound as white crystals melting at 140-141°C.

g) (4-Bromo-3-methyl-phenyl)-carbamic acid methyl ester

To a solution of 10.00 g 4-bromo-3-methylaniline in 50 mL dichloromethane was added 80 mL of a 10% solution of sodium bicarbonate in water. The mixture was cooled to 0°C and 6.2 mL (7.62 g) methyl chloroformate was added during 10 min. with stirring. The

reaction mixture was stirred at room temperature for 1h. The phases were separated. The organic phase was washed with a 10% solution of citric acid in water, 10% solution of sodium bicarbonate in water and brine, dried with magnesium sulfate and evaporated to yield 12.94 g of the title compound as light brown solid melting at 71-72°C.

Example 27

a) (R)-4,7-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride

The title compound (MS: M+H=201.2; mp.: 245°C (dec)) was produced in accordance with the general method of example 26a) from (R)-4,7-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester

HNMR: (250 MHz, DMSO-d6, δ [ppm]) 1.51 (d, J=6.5Hz, 3H); 2.43 (s, 3H); 3.50-3.74 (m, 2H); 4.36-4.58 (m, 2H); 4.74-4.89 (m, 1H); 6.34 (s, 1H); 6.82 (d, J=7Hz, 1H); 7.38(s, 1H); 7.41(d, J=7Hz, 1H).

Intermediate:

b) (R)-4,7-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester

To a solution of 1.52 g (R)-8-bromo-4,7-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester in 15 mL ethanol was added 0.15 g 10% palladium on charcoal and the mixture was stirred under a hydrogen atmosphere for 6h. A further 0.15 g 10% palladium on charcoal was added and the mixture was stirred a further 6h under a hydrogen atmosphere. Again 0.15 g 10% palladium on charcoal was added and the mixture was stirred a further 6h under a hydrogen atmosphere. The catalyst was removed by filtration over dicalite and the filtrate was evaporated. The residue was purified by chromatography on silica gel with 4:1 hexane : ethyl acetate to yield 0.59 g of the title compound as a white foam. MS: (M+H) = 301.3.

Example 28

a) (R)-4,7,8-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound (MS: M+H=215.3) was produced in accordance with the general method of example 21a) from (R)-4,7,8-trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester. The material was isolated as the free amine base

by chromatography on silica gel with dichloromethane : methanol : ammonia (9 : 1 : 0.1) in the form of a light yellow oil.

HNMR: (250 MHz, $CDCl_3$, δ [ppm]) 1.47 (d, J=6.5Hz, 3H); 2.33 (s, 3H); 2.38 (s, 3H); 3.07-3.42 (m, 2H); 4.06-4.26 (m, 2H); 4.34-4.42 (m, 1H); 6.02 (s, 1H); 7.07 (s, 1H); 7.31(s, 1H).

Intermediate

b) (R)-4,7,8-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester

To a solution of 1.18 g (R)-8-bromo-4,7-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole-2-carboxylic acid tert-butyl ester in 12 mL dioxane were added 0.36g tetrakistriphenylphosphinepalladium, 1.29 g potassium carbonate and 0.39 trimethylboroxine and the mixture was heated 1h at reflux. The reaction mixture was partitioned between water and ethyl acetate. The phases were separated and the organic phase was washed with 10% sodium bicarbonate, 10% citric acid and brine, dried over magnesium sulfate and purified by chromatography on silica gel with hexane : ethyl acetate (3 : 1) to yield 0.62 g of the title compound as slightly yellow foam. MS: (M+H) = 315.4.

Example 29

a) (R)-7-Chloro-4,8-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

The title compound, ISP-MS: m/e = 235.2 ($[M + H]^+$), was produced in accordance with the general method of example 1a) from (R)-7-chloro-4,8-dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one. Yellow foam.

Intermediate

b) (R)-7-Chloro-4,8-dimethyl-3,4-dihydro-2H-pyrazino[1,2-a]indol-1-one.

The title compound (ISP-MS: m/e = 249.2 (M^++H)) was produced in accordance with the general method of example 1b) from 6-chloro-5-methyl-1H-indole-2-carboxylic acid ethyl ester and (S)-5-methyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester. Yield: 34%. Yellow solid.

Intermediate Sulfamidate

(R,S)-5-Ethyl-2,2-dioxo-[1,2,3]oxathiazolidine-3-carboxylic acid tert-butyl ester

Prepared in the same manner as in example 1f from carbamic acid, (2-hydroxybutyl)-, 1,1-dimethylethyl ester (m.p.: 116-118°C).

EXAMPLE 30

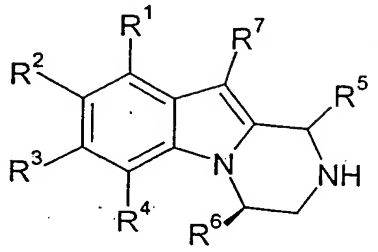
Pharmaceutical Composition

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Compound of formula I, e.g. compound of formula (I), e.g. (R)-6-Ethyl-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole	10.0 – 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

CLAIMS

1. A compound of formula (I):



(I)

wherein

R^1, R^2, R^3 and R^4 are independently selected from hydrogen, halogen, hydroxy, alkyl, cycloalkyl, arylalkyl, aryl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkylthio, arylthio, alkylsulfoxyl, arylsulfoxyl, alkylsulfonyl, arylsulfonyl, amino, nitro, cyano, alkoxycarbonyl, aryloxycarbonyl, mono- and di-alkylaminocarbonyl, alkylcarbonylamino, carboxy or heterocyclyl; with the proviso that at least one of the moieties R^1, R^2, R^3 and R^4 is not hydrogen.

R^5 is hydrogen, alkyl or cycloalkyl;

R^6 is alkyl or cycloalkyl;

R^7 is hydrogen, halogen, alkyl, cycloalkyl, hydroxyalkyl, carboxyalkyl, carbamoylalkyl, alkoxycarbonylalkyl, aryloxycarbonylalkyl, formyl, alkylcarbonyl, alkoxy or alkylthio;

and their pharmaceutically acceptable salts, solvates and esters.

2. A compound according to claim 1, wherein at least two or three of the moieties R^1, R^2, R^3 and R^4 are not hydrogen.

3. A compound according to any of claims 1 to 2, wherein at least two of the moieties R^1, R^2, R^3 and R^4 are not hydrogen.

4. A compound according to any of claims 1 to 3, wherein at least three of the moieties R^1, R^2, R^3 and R^4 are not hydrogen.

5. A compound according to claims 1 to 4, wherein R^1, R^2, R^3 and R^4 are independently selected from hydrogen, halogen, alkyl, alkoxy, haloalkoxy or haloalkyl.

6. A compound according to any of claims 1 to 5, wherein R^1, R^2, R^3 or R^4 are independently selected from hydrogen, halogen, alkyl, alkoxy, halomethyl, and halomethoxy.

7. A compound according to any of claims 1 to 6, wherein R^1, R^2, R^3 or R^4 are independently selected from hydrogen chloro, fluoro, bromo, trifluoromethyl, methyl, ethyl, methoxy and trifluoromethoxy.

8. A compound according to any one of claims 1 to 7, wherein R^5 is hydrogen or alkyl.

9. A compound according to any one of claims 1 to 8, wherein R^5 is hydrogen or methyl.

10. A compound according to any one of claims 1 to 9, wherein R^5 is hydrogen.

11. A compound according to any one of claims 1 to 10, wherein R^6 is alkyl or cycloalkyl.

12. A compound according to any one of claims 1 to 11, wherein R^6 is alkyl.

13. A compound according to any one of claims 1 to 12, wherein R^6 is methyl or ethyl.

14. A compound according to any one of claims 1 to 13, wherein R^6 is methyl.

15. A compound according to any one of claims 1 to 14, wherein R^7 is hydrogen, alkyl or alkoxy.

16. A compound according to any one of claims 1 to 15, wherein R^7 is hydrogen, methyl or methoxy.

17. A compound according to any of claims 1 to 16, wherein R^7 is hydrogen or methyl.

18. A compound according to any of claims 1 to 17, wherein R^7 is hydrogen.

19. A compound according to any one of claims 1 to 18 selected from the group consisting of

1. (R)-6-Ethyl-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
2. (R)-4-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
3. (R)-7-Bromo-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
4. (R)-7-Chloro-8-fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
5. (R)-4,8-Dimethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
6. (R)-7,9-Dichloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole
7. (R)-6-Fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
8. (R)-4,6-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
9. (R)-8-Fluoro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
10. (R)-7-Chloro-10-methoxy-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
11. (R)-7-Chloro-4,6,10-trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole oxalate;
12. (R)-7-Bromo-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
13. (R)-4-methyl-6-trifluoromethoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
14. (R)-7-Chloro-4-ethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
15. (R)-7-Chloro-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
16. (R)-4,6,9-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
17. (R)-4,6,7-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
18. (R)-7-Chloro-4,6-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
19. (R)-4,8-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
20. (R)-4,7-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole hydrochloride;
21. (R)-4,7,8-Trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole; and
22. (R)-7-Chloro-4,8-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole.

20. A compound according to any of claims 1 to 19 selected from the group consisting of

    1. (R)-6-Ethyl-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
    2. (R)-4-Methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
    3. (R)-4,8-Dimethyl-7-trifluoromethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
    4. (R)-4,6-Dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
    5. (R)-7-Chloro-10-methoxy-4-methyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole;
    6. (R)-7-Chloro-4,6,10-trimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole oxalate; and
    7. (R)-7-Chloro-4,6-dimethyl-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole.

21. A compound according to any one claims 1 to 20 for use as therapeutically active substance.

22. The use of a compound of formula (I) as set out in any of claims 1 to 20 in the manufacture of a medicament for the treatment of disorders of the central nervous system, damage to the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, type II diabetes, and sleep apnoea.

23. A use according to claim 22, wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses; schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

24. A use according to claim 23, wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

25. A use according to claim 24, wherein said toxic or infective CNS disease is encephalitis or meningitis.

26. A use according to claim 25, wherein the cardiovascular disorder is thrombosis.

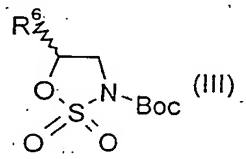
27. A use according to claim 26, wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility.

28. A use of a compound of formula (I) as set out in any of claims 1 to 27 in the manufacture of a medicament for the treatment of obesity.

29. A method of treatment of any of the disorders set out in claims 23 to 28 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 20.

30. A use or method according to any of claims 23 to 29, wherein said treatment is prophylactic treatment..

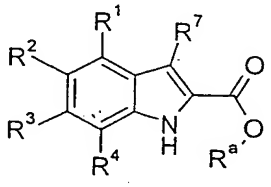
31. A process for the preparation of a compound according to any one of claims 1 to 20 comprising a reaction with a compound of formula (III)



(III)

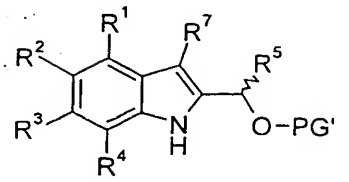
wherein R^6 is as defined in any of claims 1 to 20 with a compound selected from the group consisting of

a)



wherein R^1, R^2, R^3, R^4, and R7 are as defined in claims 1 to 20 and R^a is alkyl; and

b)



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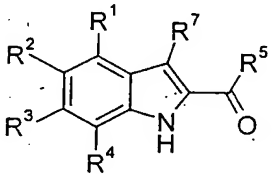
wherein R^1, R^2, R^3, R^4, R^5, and R^7 are as defined in claims 1 to 20; and PG' is hydrogen or an OH-protecting group and

c)



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wherein R^1, R^2, R^3, R^4, R^5, and R^7 are as defined above.

32. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 20 in combination with a pharmaceutically acceptable carrier or excipient.

33. A method of making a composition according to claim 32 comprising combining a compound of formula (I) as set out in any one of claims 1 to 20 with a pharmaceutically acceptable carrier or excipient.

34. A method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a compound according to any one of claims 1 to 20 and a therapeutically effective amount of a lipase inhibitor.

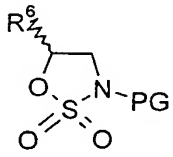
35. The method according to claim 34, wherein the lipase inhibitor is orlistat.

36. The method according to claims 34 and 35 for the simultaneous, separate or sequential administration.

37. The use of a compound according to any one of claims 1 to 20 in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor.

38. The use according to claim 37, wherein the lipase inhibitor is orlistat.

39. A compound of formula (III)



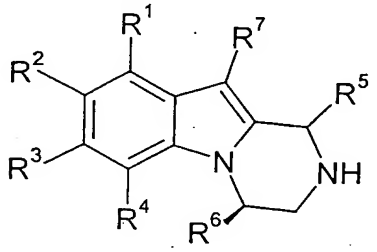
(III)

wherein R^6 is as defined in any of claims 1 to 20 and PG is a nitrogen protecting group.

40. The invention as hereinbefore described.

ABSTRACT

The present invention refers to chemical compounds of formula (I)



(I)

as well as pharmaceutically usable salts, solvates and esters thereof, wherein R^1 to R^7 have the significance given in the description and the claims. The compounds can be used in the form of pharmaceutical preparations for the treatment or prevention of disorders of the central nervous system, damage to the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, type II diabetes, obesity and sleep apnoea.

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SERIAL NO. 10/092,701
FILED: 3/07/02

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